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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,410	12/28/2000	Gloria C. Li	55672-A-PCT-US/ JPW/AJM/M	6916
57539	7590	02/03/2006	EXAMINER	
COOPER & DUNHAM LLP 1185 AVENUE OF THE AMERICAS NEW YORK, NY 10036			ZARA, JANE J	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/750,410	LI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,15,16 and 18-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,15,16,18-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 11-18-05.

Claims 1, 2, 15, 16, 18-22 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 15, 16 and 18-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 39 and 40 of copending Application No. 10/712,642 for the reasons of record set forth in the Office action mailed 8-15-05.

No arguments have been provided addressing this rejection.

New Rejections

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Takiguchi et al.

Takiguchi et al (Genomics, Vol. 35, pages 129-135, 1996) teach antisense oligonucleotides that specifically hybridize to a nucleic acid encoding a human DNA-dependent protein kinase subunit, Ku70 (see 6th and 7th full paragraphs on p. 130).

The burden of establishing whether the prior art polynucleotide has the function of encoding a fragment of a cell signaling cascade protein as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products

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[footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotides disclosed by Takiguchi et al meet all of the structural limitations of the instantly claimed invention, they would necessarily be presumed to have the functionality claimed, of specifically binding to and inhibiting the expression of human Ku70 in vitro.

Therefore, absent evidence to the contrary, claim 15 is anticipated by or, in the alternative, obvious over Takiguchi et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 15, 16 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takiguchi et al as applied to claim 15 above, Reeves et al and Milner et al, the combination in view of Au-Young et al.

The claims are drawn to compositions and methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an

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antisense oligonucleotide and optionally further comprising a ribozyme, specifically targeting a nucleic acid encoding a human DNA dependent protein kinase subunit (Ku70), which antisense inhibits the expression of the target human Ku70 subunit, and which antisense is in an appropriate expression vector, operably linked to a heat shock promoter.

Takiguchi (Genomics 35: 129-135, 1996) is relied upon as set forth in the 102/103 rejection. Takiguchi et al teach the role of mouse and human DNA-PK (comprising the subunits Ku70, Ku80 and DNA-PK catalytic subunit) in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70, Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p. 129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), and recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). Takiguchi teaches the motivation to establish experimental mouse models for studying the role of DNA-PK in human diseases (see last paragraph of the article, bridging pp. 133-134).

Reeves et al (J. Biol. Chem., Vol. 264(9): 5047-5052, 1989) teach the polynucleotide sequence encoding human DNA-PK subunit Ku70, and Ku70's binding

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to the ends of double stranded DNA in a complex with Ku80 (see especially figure 4 on p. 5050 and the text on p. 5047).

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

The primary references of Takiguchi et al, Reeves et al and Milner et al do not teach methods for increasing a target cell's sensitivity to DNA damaging agents in vitro comprising the administration of an antisense oligonucleotide specifically targeting a nucleic acid encoding Ku70, and which antisense is in an appropriate expression vector, operably linked to a heat shock promoter, and optionally linked to a ribozyme.

Au-Young et al (USPN 5,773,580) teach pharmaceutical compositions comprising antisense oligonucleotides for inhibiting a known target gene, as well as teaching expression vectors comprising antisense oligonucleotides and ribozymes, which oligonucleotides are operably linked to regulatory elements including an inducible (heat shock) promoter (see esp. col. 10-11, 20-21).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of Ku70 in vitro because its nucleotide sequence had been taught previously by Reeves et al, and Milner et al teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540). Milner

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et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides human DNA dependent protein kinase subunits, including Ku70.

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of nucleic acid constructs including antisense and ribozymes in an appropriate target cell, as taught previously by Au-Young et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector in order to control the conditions of expression of the operably linked antisense, and in order to control conditions for antisense expression and subsequent inhibition of the antisense's target gene in an appropriate target cell.

One of ordinary skill in the art would have been motivated to target and inhibit the expression of the various subunits of DNA-PK, including Ku70, in order to increase a target cell's sensitivity to DNA damaging agents because Takiguchi et al teach the relationship between increasing cell radiosensitivity or loss of DNA repair function, and

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loss of functional DNA-PK. One of ordinary skill in the art would have been motivated to inhibit the expression of Ku70 in order to increase a target cell's sensitivity to DNA repair because it was well known in the art at the time of the invention that Ku 70 is involved in double stranded DNA repair and it was also well known that strand repair occurs in cells following DNA damage (e.g. strand breaks). One of ordinary skill in the art would have expected that a cancer cell would undergo DNA repair after its exposure to DNA damaging agents. And one of ordinary skill in the art would be motivated to undermine a cancer cell's ability to repair DNA after treating it with DNA damaging agents in order to eventually undermine that cancer's ability to survive.

One of ordinary skill in the art would have expected that by utilizing appropriate conditions for expression (e.g. induction by heat), the antisense targeting DNA-PK would be expressed upon induction of the heat shock promoter because such induction systems as heat shock promoters have been routinely used as described by Au-Young et al. One of ordinary skill in the art would have been motivated to induce expression of antisense and ribozymes under desired conditions (e.g. upon exposure heat) because induction is a way of controlling the conditions for increased expression of the operably linked antisense and ribozymes, and also a way of controlling the subsequent inhibition of target gene expression following expression of these antisense. In this way, increasing a cell's sensitivity to DNA damaging agents is in turn induced following heat treatment and expression of antisense. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

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Applicant's arguments filed 11-18-05 have been fully considered but they are not persuasive. Applicant argues that the combined teachings of Takiguchi, Reeves, Milner and Au-Young fail to properly support a prima facie case of obviousness for several reasons. Applicant argues that they have made the surprising discovery of Ku70's role in DNA double stranded breaks repair and therefore the invention was not obvious. Contrary to Applicant's assertions, Takiguchi in 1996 repeatedly taught Ku70's role in DNA double stranded breaks repair. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70, Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p. 129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). So, contrary to Applicant's assertions, the role of Ku70 in DNA double strand breaks repair was not a surprising finding at the time the instant application was filed.

Applicant argues that Takiguchi teaches mouse and not human Ku70 and that since the relationship between mouse and human Ku70 has not been established, Takiguchi cannot render the instant invention obvious. Contrary to Applicant's assertions, Takiguchi teach the role of mouse and human DNA-PK in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function. Takiguchi teaches the DNA-dependent protein kinase (DNA-PK) comprising Ku70,

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Ku80 and the DNA-PK catalytic subunit, which DNA-PK functions in DNA double-strand break repair (see 1st & 3rd full paragraph on p. 129). Takiguchi also teaches that the Ku70/80 heterodimer portion of the DNA-PK binds with high affinity to the end of double stranded DNA, and to a single stranded DNA transition (see 2nd full paragraph on p. 129), and recruits and activates the DNA catalytic subunit of the DNA-PK (see 3rd full paragraph on p. 129). Takiguchi teaches the role of Ku70 in DNA double strand repair (see bridging paragraph, pp. 133-134). Takiguchi teaches the motivation to establish experimental mouse models for studying the role of DNA-PK in human diseases (see last paragraph of the article, bridging pp. 133-134). Takiguchi therefore teaches a motivation to inhibit either mouse DNA-PK or human Ku70 in DNA-PK activity to study its role in human diseases, including the ability of a cell with DNA damage to repair strand breaks. This motivation, combined with the routine approach taught by Milner to design and test antisense in their ability to target and inhibit the expression of a target gene of known sequence (e.g. human Ku70) in vitro, renders the invention obvious.

Applicant argues that none of the cited references teaches the introduction of any antisense oligonucleotide into any cell for the purpose of increasing the susceptibility of the cell to DNA damaging agents. Applicant is correct that none of the references alone anticipates the claimed invention. The combined teachings, however, render the instant invention obvious. Takiguchi provides the motivation to target and inhibit the expression of Ku70 in humans (or in a mouse model) to study its role in various human diseases, and to study the role of Ku70 in DNA-PK's ability to repair strand breaks. It was well known in the art that when damaging agents are used to treat cells, strand breaks

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occur. Milner taught the routine approach to design and test antisense inhibition in a cell in vitro and Reeves teaches the nucleotide sequence of the target gene. It therefore would have been obvious to one of ordinary skill in the art to design antisense to inhibit the expression of the well known target gene Ku70 in vitro to study its role in repairing DNA strand breaks. It would have been obvious to compare the effect of DNA damaging agents on cells that have Ku70 expression with cells that lack Ku70 expression following the inhibition by antisense. For these reasons, the combined teachings of Takiguchi, Reeves, Milner and Au-Young render the instant invention obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 15, 16, 18-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising an antisense oligonucleotide that specifically hybridizes with and inhibits the expression of human Ku70. The scope of the claims includes numerous structural variants (e.g. hundreds of

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possible sequences) and the genus is highly variant because a significant number of structural differences between members of the given genus is permitted. Concise structural features (antisense or ribozyme sequences) that distinguish structures within the genus from those without are missing from the disclosure and the claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the various genera claimed, drawn to antisense or ribozymes that specifically target and inhibit the expression of Ku70 in a cell. Thus, Applicant was not in possession of the claimed genus.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding

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this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
1-31-06

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